

# Oxygenation and Ventilation for Children

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The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations in this section were informed by recommendations from the Surviving Sepsis Campaign's guidelines for managing [adult sepsis](#), [pediatric sepsis](#), and [COVID-19](#), as well as by recommendations from the 2015 Pediatric Acute Lung Injury Consensus Conference ([PALICC](#)).

## Goal of Oxygenation

### Recommendations

- An oxygen saturation ( $\text{SpO}_2$ ) target of 92% to 97% is recommended for most children with COVID-19 who require supplemental oxygen (**AIIb**).
- For children with severe pediatric acute respiratory distress syndrome (PARDS; i.e., with an oxygenation index  $\geq 16$  or  $\text{SpO}_2$  index  $\geq 12.3$ ), an  $\text{SpO}_2$  of  $<92\%$  can be considered to minimize exposure to a high fraction of inspired oxygen ( $\text{FiO}_2$ ), but prolonged periods of  $\text{SpO}_2 < 88\%$  should be avoided (**CIII**).

### Rationale

The optimal  $\text{SpO}_2$  in children with COVID-19 is unknown. However, there is no evidence that the target  $\text{SpO}_2$  should differ from the 2015 PALICC recommendation.<sup>1</sup> An  $\text{SpO}_2$  of 92% to 97% is recommended for most children with COVID-19 who require supplemental oxygen. The potential harm of hyperoxia in children was demonstrated in a recent meta-analysis of 11 observational studies of children without COVID-19.<sup>2</sup> The study demonstrated that critically ill children with hyperoxia had greater odds of mortality than those without hyperoxia (OR 1.59; 95% CI, 1.00–2.51). However, there was significant heterogeneity across the included studies for populations, definitions of hyperoxia, and the timing of assessment for mortality outcomes. For children with severe PARDS (i.e., with an oxygenation index  $\geq 16$  or  $\text{SpO}_2$  index  $\geq 12.3$ ),<sup>1</sup> an  $\text{SpO}_2 < 92\%$  can be considered to minimize exposure to a high  $\text{FiO}_2$ . Although no evidence clearly identifies a safe minimum  $\text{SpO}_2$  in children, prolonged exposure to  $\text{SpO}_2 < 88\%$  should be avoided. When  $\text{SpO}_2$  is  $< 92\%$ , monitoring oxygen delivery markers, including central venous  $\text{SpO}_2$ , is suggested.<sup>3</sup>

## High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation for Children With COVID-19 and Acute Respiratory Failure

### Recommendation

- For infants and children with COVID-19 and persistent respiratory failure despite conventional oxygen therapy who have no indicators for endotracheal intubation, a time-limited trial of noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) oxygen is recommended (**AIIa**). There is insufficient evidence for the Panel to recommend either for or against the use of HFNC oxygen over NIV or the use of NIV over HFNC oxygen in infants and children with COVID-19.

### Rationale

No high-quality studies evaluate the use of HFNC oxygen or NIV in children with COVID-19. Therefore, when choosing a mode of respiratory support for children with COVID-19, the principles of management used for patients without COVID-19 should be followed. Both the *Surviving Sepsis*

*Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children* and PALICC recommend the use of NIV for children with respiratory failure who have no indication for intubation.<sup>4,5</sup>

Furthermore, the response to NIV, particularly for children with more severe hypoxemia or high work of breathing, should be gauged early (within the first several hours). If the patient does not show improvement, intubation should be considered. To unload respiratory muscles, bilevel modes of NIV (with inspiratory pressure augmentation, such as BiPAP), if tolerated, are preferred over the use of continuous positive airway pressure (CPAP) alone, although CPAP is an alternative for children who cannot achieve an adequate seal with the NIV interface or who have significant patient-ventilator asynchrony.<sup>4</sup>

HFNC oxygen is a relatively new, but increasingly used, mode of respiratory support for infants and children with acute respiratory failure.<sup>6</sup> Data from studies evaluating the effectiveness of HFNC oxygen relative to NIV or conventional oxygen are limited to studies of children with pneumonia in limited-resource settings and studies of children with bronchiolitis. Two randomized controlled trials of children with pneumonia were conducted in limited-resource settings. One study demonstrated a slightly lower relative risk of mortality with the use of HFNC oxygen when compared with conventional oxygen therapy (adjusted HR 0.79; 95% CI, 0.54–1.16), although the results were not statistically significant.<sup>7</sup> The other trial demonstrated that children treated with bubble CPAP ventilation had a lower proportion of mortality than children who received low-flow oxygen (relative risk 0.25; 95% CI, 0.07–0.89;  $P = 0.02$ ).<sup>8</sup> The results also indicated that for the composite outcome of treatment failure, there was no difference between the use of HFNC oxygen and bubble CPAP (relative risk 0.50; 99.7% CI, 0.11–2.29).

A randomized, noninferiority trial compared HFNC oxygen (2 L/kg/min) and nasal CPAP among 142 infants aged <6 months with bronchiolitis not caused by COVID-19.<sup>9</sup> The primary outcome was treatment failure within 24 hours, defined as an increase of  $\geq 1$  point in the modified Wood's Clinical Asthma Score (M-WCAS) or Échelle Douleur Inconfort Nouveau-Né (EDIN) score (a neonatal pain and discomfort scale), a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour. Treatment failure occurred more often in the HFNC oxygen arm than in the nasal CPAP arm (51% vs. 31%), a result that failed to meet the prespecified noninferiority margin. Notably, in the HFNC arm, 72% of the patients who had treatment failure were managed successfully with nasal CPAP, and there were no differences between the arms for intubation rates or length of stay.

A systematic review of the noninferiority trial and 2 smaller trials comparing HFNC to nasal CPAP summarized the results of 213 infants and children aged  $\leq 2$  years with bronchiolitis.<sup>10</sup> Treatment failure in the 2 smaller trials was rare, and no differences were detected between the HFNC and nasal CPAP arms for any of the clinical outcomes.<sup>11,12</sup>

In a study that assessed whether higher flow rates of HFNC oxygen improved outcomes, 286 infants aged  $\leq 6$  months and with severe bronchiolitis were randomized to receive HFNC oxygen 2 L/kg/min or HFNC oxygen 3 L/kg/min.<sup>13</sup> The primary outcome of treatment failure (i.e., an increase of  $\geq 1$  point in M-WCAS or EDIN score, a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour) occurred in 38.7% of the infants in the 2 L/kg/min arm and in 38.9% of the infants in the 3 L/kg/min arm ( $P = 0.98$ ). Patient discomfort, as measured by EDIN score, occurred more often in the 3 L/kg/min arm than in the 2 L/kg/min arm (43% vs. 16%,  $P = 0.002$ ).

HFNC oxygen is increasingly being used in children. These studies highlight the potential role of an HFNC oxygen trial in the management of children with acute respiratory failure due to COVID-19, particularly for infants and young children who may have NIV-related challenges, such as poor mask

fit, discomfort, or patient-ventilator asynchrony. For the use of HFNC oxygen in children, consider flow rates of up to 2 L/kg/min, with a maximum of 60 L/min. If patients do not improve within the first few hours of receiving HFNC oxygen, their treatment should be escalated to NIV or intubation.

## Awake Prone Positioning for Children Not Receiving Mechanical Ventilation

### *Recommendations*

- There is insufficient evidence for the Panel to recommend either for or against a trial of awake prone positioning for children with persistent hypoxemia who require HFNC oxygen or NIV and do not require endotracheal intubation.
- For patients with refractory hypoxemia who meet the indications for intubation and mechanical ventilation, the Panel **recommends against** the use of awake prone positioning as a rescue therapy to avoid intubation (**AIII**).

### *Rationale*

There are no high-quality pediatric data evaluating the effect of awake prone positioning on clinical outcomes in children with COVID-19 or non-COVID-19-related illness. Awake prone positioning may be considered for older children and adolescents (see [Oxygenation and Ventilation for Adults](#)). In addition, pediatric clinicians should consider a child's developmental stage and ability to comply with the protocols for awake prone positioning.

## Intubation for Mechanical Ventilation in Children With Acute COVID-19

### *Recommendations*

- If intubation becomes necessary, the Panel recommends that an experienced practitioner perform the procedure in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation (**AIII**).
- The Panel recommends using cuffed endotracheal tubes over uncuffed endotracheal tubes in children who require endotracheal intubation (**AIIb**).

### *Rationale*

To optimize the safety of patients and health care workers and maximize first-attempt success, intubation should be performed in a controlled setting by an experienced practitioner. In addition, cuffed endotracheal tubes are preferred for children of all ages with COVID-19 to minimize leak around the endotracheal tube, ensure delivery of ventilator pressure, decrease the risk of aspiration, reduce the need for endotracheal tube exchange, and reduce aerosolization of respiratory secretions during mechanical ventilation.<sup>3,14-16</sup>

## General Considerations for Children With COVID-19 and PARDS Who Require Mechanical Ventilation

### *Recommendations*

For children with COVID-19 and PARDS who require mechanical ventilation:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (**AIIb**).
- The Panel recommends targeting plateau pressures of  $\leq 28$  cm H<sub>2</sub>O for children with normal chest wall compliance and  $\leq 32$  cm H<sub>2</sub>O for those with impaired chest wall compliance (**AIII**).

- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy (i.e., >10–15 cm H<sub>2</sub>O or higher in patients with severe PARDS) over a lower PEEP strategy, titrated based on observed responses in oxygenation, hemodynamics, and respiratory system compliance (**BIIB**).
- The Panel recommends permissive hypercapnia (e.g., pH >7.15 to 7.30), if needed, to remain within lung-protective strategies and to minimize ventilator-associated lung injury, provided the patient does not have a coexisting condition that would be worsened by acidosis (e.g., severe pulmonary hypertension, ventricular dysfunction, intracranial hypertension) (**AIII**).
- The Panel **recommends against** the routine use of inhaled nitric oxide (**AIII**).

### ***Rationale***

There is no evidence that ventilator management of children with PARDS due to COVID-19 should differ from ventilator management of patients with PARDS due to other causes. The Panel's recommendations are derived from the 2015 PALICC recommendations.<sup>1,3</sup> Since the publication of the PALICC recommendations, no randomized trials have provided significant new evidence, although some observational data support some of the PALICC recommendations.

A large observational study conducted in 71 international pediatric intensive care units identified that for patients with mild to moderate acute respiratory distress syndrome (ARDS), less adherence to the recommended VT of 5 mL/kg to 8 mL/kg (or 3 mL/kg to 6 mL/kg for patients with severe ARDS) was associated with higher mortality and with more time on ventilation.<sup>17</sup> In general, supraphysiologic VT ventilation (>8 mL/kg) should not be used in patients with PARDS, and VT should be adjusted within the acceptable range to maintain other lung-protective ventilation targets (e.g., maintaining ≤28 cm H<sub>2</sub>O plateau pressure). The use of ultra-low VT ventilation (<4 mL/kg) has not been systematically studied in children, so it should be used with caution.

The ARDS Network established a ventilator protocol that includes suggested low PEEP/high FiO<sub>2</sub> levels.<sup>18</sup> The protocol suggests that for patients receiving FiO<sub>2</sub> ≥0.6, a PEEP level of ≥10 cm H<sub>2</sub>O would be implemented, which aligns with recommendations from PALICC. Two observational studies have identified better clinical outcomes associated with use of the suggested (or higher) PEEP levels compared to lower PEEP levels.<sup>17,19</sup> The multicenter studies, including nearly 1,500 pediatric patients with ARDS, each demonstrated that PEEP levels lower than those recommended by the ARDS Network were associated with higher mortality.

Inhaled nitric oxide can be considered as a rescue therapy for children with severe PARDS and COVID-19. In a small, randomized trial, the use of inhaled nitric oxide resulted in reduced use of extracorporeal membrane oxygenation (ECMO).<sup>20</sup> However, inhaled nitric oxide has a heterogeneous treatment effect, and many patients do not show improved gas exchange. Although adverse effects are rare, use of inhaled nitric oxide can have a substantial effect on health care costs. Therefore, inhaled nitric oxide should not be considered routine therapy for children with PARDS or COVID-19 who are receiving mechanical ventilation.

## **Fluid Management for Children With PARDS**

### ***Recommendation***

- Following an initial resuscitation in children with PARDS due to COVID-19, clinicians should monitor and titrate fluid balance to maintain adequate intravascular volume while aiming to prevent positive fluid balance (**BIIB**).

## ***Rationale***

There is no evidence that fluid management in children with PARDS due to COVID-19 should differ from fluid management in patients with PARDS due to other causes. Therefore, the Panel's recommendation aligns with the PALICC recommendation.<sup>1</sup> No pediatric randomized trials have directly compared a liberal versus conservative fluid strategy in PARDS of any etiology. Several observational studies have demonstrated an association between greater fluid overload and worse clinical outcomes, including fewer ventilator-free days and increased mortality.<sup>21-23</sup>

In a multicenter study of 168 children with acute lung injury, daily and cumulative fluid balance were measured over the first 7 days after participants met the inclusion criteria. After adjustment for demographic characteristics, pediatric risk of mortality III (PRISM III) scores, vasopressor use, and the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ), an increasing cumulative fluid balance on Day 3 was associated with fewer ventilator-free days, but no association with mortality was detected.<sup>21</sup>

A more recent, single-center study including 732 children with acute lung injury demonstrated an association between higher cumulative fluid balance on Days 5 to 7 and increased mortality (for 100 mL/kg on Day 5; OR 1.34; 95% CI, 1.11–1.61) after adjustment for oxygenation index, the number of nonpulmonary organ failures, immunocompromised status, and vasopressor scores. Also, greater cumulative fluid balance on Days 4 to 7 was associated with a lower probability of successful extubation by Day 28.<sup>23</sup> Collectively, the findings from these pediatric observational studies demonstrate the potential harm of fluid overload in children with PARDS, particularly after 3 to 4 days of illness.

These results are consistent with the findings from FACTT, a trial of conservative versus liberal fluid management strategies in adults.<sup>24</sup> In adults, FACTT found no difference between arms for 60-day mortality, but the conservative strategy arm demonstrated improved oxygenation and less time on mechanical ventilation and in the intensive care unit when compared with the liberal strategy arm. However, no analysis of data from prospective pediatric trials delineates a causal relationship between a specific, protocolized, fluid management strategy, or the timing of such a strategy, and clinical outcomes. Therefore, an individualized fluid management approach that is titrated to maintain intravascular volume while preventing excessive positive fluid balance, as suggested by the 2015 PALICC recommendation, is appropriate.<sup>1</sup>

## **Neuromuscular Blockade for Mechanically Ventilated Children With Severe PARDS**

### ***Recommendation***

- For mechanically ventilated children with severe PARDS and COVID-19, the Panel recommends minimal yet effective use of neuromuscular blocking agents in conjunction with sedation, if sedation alone is inadequate to achieve lung-protective ventilation (**BIII**).

### ***Rationale***

There is no evidence that the use of neuromuscular blockade in children with COVID-19 should differ from practices used for severe PARDS from other causes. Therefore, the Panel's recommendation aligns directly with the PALICC recommendation.<sup>1</sup> Since the publication of the 2015 PALICC recommendation, no new data support significant changes to the recommendation.



## Therapies for Mechanically Ventilated Children With Severe PARDS and Refractory Hypoxemia

### *Recommendations*

For children with severe PARDS and refractory hypoxemia after other oxygenation strategies have been optimized:

- The Panel recommends inhaled nitric oxide as a rescue therapy; if no rapid improvement in oxygenation is observed, inhaled nitric oxide should be discontinued (**BIIB**).
- The Panel recommends prone positioning for 12 to 16 hours per day over no prone positioning (**BIII**).
- There is insufficient evidence for the Panel to recommend either for or against the use of recruitment maneuvers, but if they are used in children, slow, incremental and decremental adjustments in PEEP are preferred to sustained inflation maneuvers.
- There is insufficient evidence for the Panel to recommend either for or against the use of high-frequency oscillatory ventilation (HFOV) in children with PARDS.

### *Rationale*

There is no evidence that the use of inhaled nitric oxide, prone positioning, or HFOV in children with COVID-19 should differ from practices used for severe PARDS from other causes. Therefore, the Panel's recommendations are largely based on PALICC recommendations.<sup>1</sup> Since the publication of the 2015 PALICC recommendations, many new trials evaluating these practices have been conducted.

One randomized controlled trial and 2 propensity-matched, observational studies have evaluated the use of inhaled nitric oxide in PARDS since the publication of the PALICC recommendations. The randomized controlled trial included 55 patients and found that the use of inhaled nitric oxide resulted in no statistical difference between arms for 28-day mortality (8% mortality in the inhaled nitric oxide arm vs. 28% in the placebo arm), although the trial was underpowered for this outcome.<sup>20</sup> However, the inhaled nitric oxide arm had approximately 5 more ventilator-free days than the placebo arm, a result that was primarily mediated by avoiding the use of ECMO. These results have been corroborated by observational studies, which also reported more ventilator-free days for patients who received inhaled nitric oxide.<sup>25,26</sup> Although the evidence is insufficient to recommend the use of inhaled nitric oxide for all patients with ARDS, in cases of severe hypoxemia, it can be considered as a rescue therapy to potentially avoid the use of ECMO.

No new studies have evaluated the role of prone positioning in PARDS, although a large, multicenter trial is ongoing. Therefore, the Panel's recommendation to consider prone positioning in cases of severe PARDS aligns with the PALICC recommendation and is supported by adult data, primarily from PROSEVA, a trial on prone positioning in patients with ARDS.<sup>27</sup>

The 2015 PALICC recommendations included the use of careful recruitment maneuvers with incremental and decremental adjustments in PEEP.<sup>1</sup> In children, this approach to recruitment maneuvers is preferred over sustained inflation maneuvers due to the increased risk of harm from barotrauma and hemodynamic compromise in patients with sustained inflation. Clinical trials in adults have highlighted the potential harm from recruitment maneuvers applied to patients who may not have recruitable lung.<sup>28,29</sup> Therefore, although there is insufficient evidence to recommend for or against the use of recruitment maneuvers in children with refractory hypoxemia, if recruitment maneuvers are used, the preferred strategy is slow, incremental increases and decreases of PEEP.

Since the publication of the 2015 PALICC recommendations, 2 small randomized controlled trials have examined the use of HFOV for PARDS.<sup>30,31</sup> Neither study found a significant difference for mortality. Several observational studies using propensity matching have shown either no difference in outcomes between the HFOV and conventional ventilation arms or a potential for higher mortality or a longer ventilation time with the use of HFOV, when compared with conventional ventilation.<sup>32-36</sup> In some of these analyses, residual confounding has been a concern. A large, multicenter randomized controlled trial of HFOV for PARDS is ongoing. Therefore, the Panel has determined that there is insufficient evidence to recommend for or against the use of HFOV in COVID-19-related PARDS. Some concerns have been raised about the use of HFOV and aerosolization of COVID-19, although adding a filter to the expiratory limb of the HFOV circuit may alleviate these concerns.

## Multisystem Inflammatory Syndrome in Children

More than half of the patients with multisystem inflammatory syndrome in children (MIS-C) require mechanical ventilation or NIV.<sup>37-39</sup> For these patients with MIS-C, the indications for mechanical ventilation vary and include shock or cardiac dysfunction, pulmonary edema, procedural preparation (e.g., to facilitate sedation for central venous catheter placement), respiratory failure, or neurologic failure. The management of oxygenation and ventilation in children with MIS-C should follow the usual principles of shock management outlined in the Surviving Sepsis Campaign guidelines for children, as well as the principles for clinical management of heart failure and general critical care, as appropriate.<sup>5</sup>

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